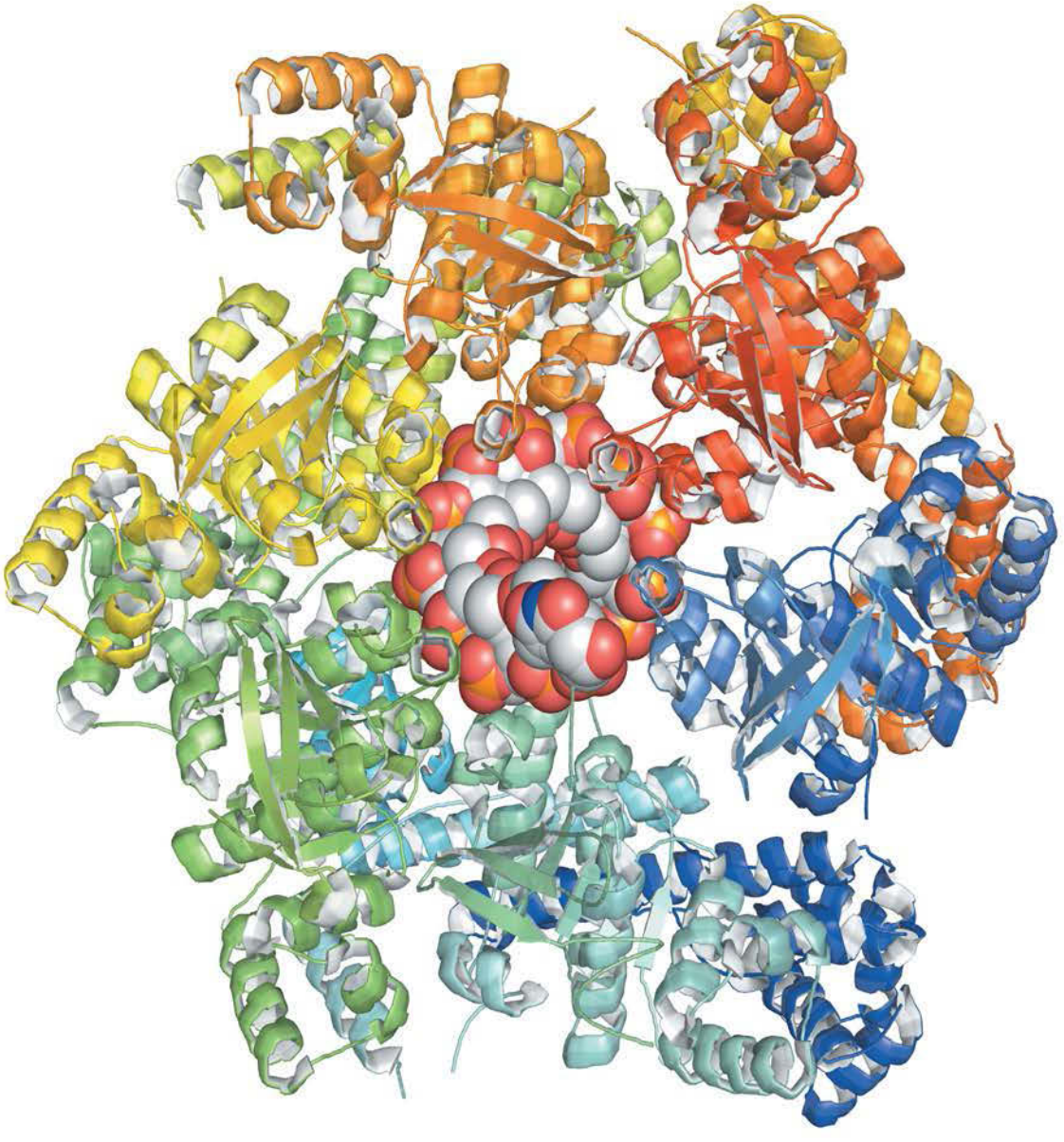
# biochemistry



Reginald H. Garrett | Charles M. Grisham

SIXTH EDITION

# biochemistry

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University of Virginia

With molecular graphic images
by Michal Sabat, University of Virginia

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*To our grandchildren Jackson, Bella, Reggie, Ricky, Charlotte Mayberry, and Ann Clara, and to the generations to follow...*

# ABOUT THE AUTHORS

Reginald H. Garrett was educated in the Baltimore city public schools and at the Johns Hopkins University, where he received his Ph.D. in biology in 1968. Since that time, he has been at the University of Virginia, where he is currently Professor Emeritus of Biology. He is the author of previous editions of *Biochemistry*, as well as *Principles of Biochemistry* (Cengage, Brooks/Cole), and numerous papers and review articles on the biochemical, genetic, and molecular biological aspects of inorganic nitrogen metabolism. His research interests focused on the pathway of nitrate assimilation in filamentous fungi. His investigations contributed substantially to our understanding of the enzymology, genetics, and regulation of this major pathway of biological nitrogen acquisition. More recently, he has collaborated in systems approaches to the metabolic basis of nutrition-related diseases. His research has been supported by the National Institutes of Health, the National Science Foundation, and private industry. He is a former Fulbright Scholar at the Universität für Bodenkultur in Vienna, Austria and served as Visiting Scholar at the University of Cambridge on two separate occasions. During the second, he was Thomas Jefferson Visiting Fellow in Downing College. In 2003, he was Professeur Invité at the Université Paul Sabatier/Toulouse III and the Centre National de la Recherche Scientifique, Institute for Pharmacology and Structural Biology in France. He taught biochemistry at the University of Virginia for 46 years. He is a member of the American Society for Biochemistry and Molecular Biology.

Charles M. Grisham was born and raised in Minneapolis, Minnesota, and educated at Benilde High School. He received his B.S. in chemistry from the Illinois Institute of Technology in 1969 and his Ph.D. in chemistry from the University of Minnesota in 1973. Following a postdoctoral appointment at the Institute for Cancer Research in Philadelphia, he joined the faculty of the University of Virginia, where he is Professor of Chemistry. He is the author of previous editions of *Biochemistry* and *Principles of Biochemistry* (Cengage, Brooks/Cole), and numerous papers and review articles on active transport of sodium, potassium, and calcium in mammalian systems, on protein kinase C, and on the applications of NMR and EPR spectroscopy to the study of biological systems. He has also authored *Interactive Biochemistry CD-ROM and Workbook*, a tutorial CD for students. His work has been supported by the National Institutes of Health, the National Science Foundation, the Muscular Dystrophy Association of America, the Research Corporation, the American Heart Association, and the American Chemical Society. He is a Research Career Development Awardee of the National Institutes of Health, and in 1983 and 1984 he was a Visiting Scientist at the Aarhus University Institute of Physiology Denmark. In 1999, he was Knapp Professor of Chemistry at the University of San Diego. He has taught biochemistry, introductory chemistry, and physical chemistry at the University of Virginia for more than 40 years. He is a member of the American Society for Biochemistry and Molecular Biology.

Georgia Cobb Garrett

Charles M. Grisham and Reginald H. Garrett

# ACTIVEMODELS LIBRARY OF PROTEINS AND NUCLEIC ACIDS

ActiveModels presents an online library of macromolecular structures with accompanying scripts detailing descriptions of structure-function relationships for the key proteins and nucleic acids mentioned in the book and listed below. The hyperlinked text controls the graphic display and presents a variety of perspectives and features. End-of-chapter problems written specifically to utilize this resource appear in most chapters.

Abl Kinase
Acetylcholinesterase (Recombinant Human)
Acetyl-CoA Carboxylase (Carboxyltransferase Domain)
AcrB Channel
Actin
Acyl-CoA Dehydrogenase
Acyl-CoA Oxidase
Adenylosuccinate Lyase
$\beta$-Adrenergic Receptor
Alcohol Dehydrogenase
Aldose Reductase
$\alpha$-Amylase (salivary)
Amyloid beta-Peptide (A$\beta$)
Androgen Receptor
Angiotension-1 Converting Enzyme (ACE)
Anthrax Lethal Factor
Apoptosis-Inducing Factor
Aprotinin
Aqp1 Aquaporin (Water Channel)
ASAP3 (ARF GTPase)
ATP/ADP Translocase-1
Atrial Natriuretic Peptide Receptor
Autotransporter (bacterial)
BiP Chaperone
Bone Morphogenetic Protein 2
Bone Morphogenetic Protein Domain
BRCA 2
BtuB (Cobalamin transporter)
Calmodulin
Caspase-6
Cat Allergen
Choline Acetyltranferase
Chorismate Mutase
Complex 1 (Electron Transport)
Complex 2 (Electron Transport)
Concanavalin
C-Reactive Protein (human)
Cu,Zn Superoxide Dismutase (human)
Cyclin-Dependent Kinase-2 (human)
Cyclooxygenase
Cystic Fibrosis Transmembrane Conductance Regulator
Cytidine Triphosphate Synthetase
Cytochrome *b* Reductase
Cytochrome *c*
Cytochrome *c* Oxidase (*Bos taurus*)
Cytochrome *c* Oxidase (*Rhodobacter sphaeroides*)
D2 Domain of NSf
Dicer I
Di-Heme Cytochrome *c*
3,4-Dihydroxyphenylalanine Decarboxylase
DNA Polymerase $\eta$
DrrA Guanine Nucleotide Exchange Factor
Dual Specificity Phosphatase 6
E1 Helicase
E1 Ubiquitin-like Protein Complex
EGFR Kinase Domain
Elastase
Enolase
Enoyl-CoA Hydratase
Estrogen Receptor
Farnesyl Transferase
Fatty Acid Transporter
Ferritin (human) and Bacterioferritin
Ferritin H Chain (human)
Ferrochelatase (human)
Fibrin (human)
FKBP12-Rapamycin Complex
Flavodoxin
FliG (Flagellar Rotor Protein)
Fructose-1-6-Bisphosphatase
GABA Receptor Associated Protein
Galectin 1 (human)
Glucose-6-Phosphate Dehydrogenase
Glutamine Synthetase
Glycogen Phosphorylase
GMP Synthetase
Grb2 Growth Factor Bound Protein 2 Signal Transduction Adaptor
GRD19p
GroEL-GroES Complex
Hemoglobin S

Hepatocyte Nuclear Factor 1b Bound to DNA
Hexokinase (human)
HIV-1 Protease
HIV Reverse Transcriptase with a Rival Purine Inhibitor
HIV Reverse Transcriptase with Inhibitor 7
HLA A2 Class I MHC
HMG-CoA Reductase
Hsp90
Influenza Virus Hemagglutinin
Interleukin 17 Receptor Complex
Interleukin -4 and its Receptor
Ire1 (Transmembrane Serine/Threonine Kinase)
Isocitrate Dehydrogenase
ITK-Sh2 Domain Bound to Phosphopeptide
KIF1A (monomeric kinesin)-Microtubule Complex)
Kinesin
Kinesin (rat)
$\beta$-Lactamase
Lactate Dehydrogenase (Malarial)
LDL Receptor
Lipocalin (human)
Luciferase Inhibitor Complex (firefly)
Lysine Gingipain (Kgp) protein
Malonyl-CoA-ACP Transferase
MDM2 (Ubiquitin-Protein Ligase E3)
Metalloprotease
Methemoglobin (horse)
Monoamine Oxidase B (human)
Myoglobin
Myosin 2 - heavy and light chain
Myosin 2 - heavy chain
Myosin 5
Nc6.8 (monoclonal Ab) Fab In Complex With Sweetener Sc45647
Neuropsin (a Serine Protease)
Nicotinic Acetylcholine Receptor
Niemann-Pick C1: Cholesterol
Nitrogenase Reductase
N-Myristoyltransferase With Bound Myristoyl-CoA
NSE/NS4A Protease Apostructure (Hepatitis C Virus)
Nuclear Receptor X Heterodimers
2,3-Oxidosqualene Cyclase with Lanosterol
p53-DNA Complex (p53 DNA-Binding Domain)
Pepsin + DMSO
P-Glycoprotein (MDR)
Phosphofructokinase *(Trypanosoma)*
Phosphoglucoisomerase *(Bacillus)*

# LABORATORY TECHNIQUES IN BIOCHEMISTRY

All of our knowledge of biochemistry is the outcome of experiments. For the most part, this text presents biochemical knowledge as established fact, but students should never lose sight of the obligatory connection between scientific knowledge and its validation by observation and analysis. The path of discovery by experimental research is often indirect, tortuous, and confounding before the truth is realized. Laboratory techniques lie at the heart of scientific inquiry, and many techniques of biochemistry are presented within these pages to foster a deeper understanding of the biochemical principles and concepts that they reveal.

### Recombinant DNA Techniques

Restriction endonuclease digestion of DNA Section 10.6d
Restriction mapping Section 10.6e–f
Nucleotide sequencing Section 11.1
Nucleic acid hybridization Section 11.3
Chemical synthesis of oligonucleotides Section 11.6
Cloning; recombinant DNA constructions Section 12.1
Construction of genomic DNA libraries Section 12.2
Combinatorial libraries of synthetic oligomers Section 12.2
Screening DNA libraries by colony hybridization Section 12.2b
mRNA isolation Section 12.2e
Construction of cDNA libraries Section 12.2e
Expressed sequence tags Section 12.2e
Southern blotting Section 12.2e
Gene chips (DNA microarrays) Section 12.2f
Protein expression from cDNA inserts Section 12.3
Screening protein expression libraries with antibodies Section 12.3a
Two-hybrid systems to identify protein:protein interactions Section 12.3c
Reporter gene constructs Section 12.3b
Polymerase chain reaction (PCR) Section 11.1b
RT-qPCR (real-time quantitative PCR) Section 12.3a
In vitro mutagenesis Section 12.3d
ChIP-Seq (chromatin immunoprecipitation-DNA sequencing) Section 12.3c
RNAi Section 12.4
DNA laser printing Section 12.5b
BioBricks Section 12.7b
CRISPR/Cas9 Section 12.7e

### Probing the Function of Biomolecules

Green fluorescent protein Section 4.3
Plotting enzyme kinetic data Section 13.3j
Enzyme inhibition Section 13.4
Optical trapping to measure molecular forces Section 16.2c
Isotopic tracers as molecular probes Section 17.4b
RNAi Section 12.4
NMR spectroscopy Section 17.4c
Transgenic animals Section 28.8
DNA footprinting Section 28.1

### Techniques Relevant to Clinical Biochemistry

Gene therapy Section 12.6a
Metabolomic analysis Section 17.5
Fluxomics Section 17.5
Tumor diagnosis with positron emission tomography (PET) Section 18.7
Glucose monitoring devices Section 22.1
Fluoro-substituted analogs as therapeutic agents Section 26.8
"Knockout" mice Section 28.7

### Isolation/Purification of Macromolecules

Ion exchange chromatography Section 5.2
Protein purification protocols Section 5.2
Dialysis and ultrafiltration Section 5.2
Size exclusion chromatography Section 5.2
SDS-polyacrylamide gel electrophoresis Section 5.2
Isoelectric focusing Section 5.2
Two-dimensional gel electrophoresis Section 5.2
Hydrophobic interaction chromatography Section 5.2
High-performance liquid chromatography Section 5.2
Affinity chromatography Section 5.2
Ultracentrifugation Section 5.2
Fractionation of cell extracts by centrifugation Section 5.2
Proteomic analysis by MudPIT (Multidimensional Protein Identification Technology) Section 5.9b

### Analyzing the Physical and Chemical Properties of Biomolecules

Titration of weak acids Section 2.2a
Preparation of buffers Section 2.3
Measurement of standard reduction potentials Section 3.9
Edman degradation Section 4.3
Nuclear magnetic resonance (NMR) Section 4.5
Estimation of protein concentration Section 5.2
Amino acid analysis of proteins Section 4.6
Amino acid sequence determination Section 5.4
Mass spectrometry of proteins Section 5.4i
Peptide mass fingerprinting Section 5.4i
Solid-phase peptide synthesis Section 5.6
Membrane lipid phase transitions Section 9.4b
DNA nanotechnology Section 10.5a
Nucleic acid hydrolysis Section 10.6
DNA sequencing Section 11.1
Single-molecule DNA sequencing Section 11.1
Density gradient (isopycnic) centrifugation Section 11.3

## The Sixth Edition

Scientific understanding of the molecular nature of life is growing at an astounding rate. Significantly, society is the prime beneficiary of this increased understanding. Cures for diseases, better public health, remedies for environmental pollution, and the development of cheaper and safer natural products are just a few practical benefits of this knowledge.

In addition, this expansion of information fuels, in the words of Thomas Jefferson, *"the illimitable freedom of the human mind."* Scientists can use the tools of biochemistry and molecular biology to explore all aspects of an organism—from basic questions about its chemical composition, through inquiries into the complexities of its metabolism, its differentiation and development, to analysis of its evolution and even its behavior. *New procedures based on the results of these explorations lie at the heart of the many modern medical miracles.* Biochemistry is a science whose boundaries now encompass all aspects of biology, from molecules to cells, to organisms, to ecology, and *to all aspects of health care.* This sixth edition of *Biochemistry* embodies and reflects the expanse of this knowledge. We hope that this new edition will encourage students to ask questions of their own and to push the boundaries of their curiosity about science.

## Making Connections

As the explication of natural phenomena rests more and more on biochemistry, its inclusion in undergraduate and graduate curricula in biology, chemistry, and the health sciences becomes imperative. The challenge to authors and instructors is a formidable one: how to familiarize students with the essential features of modern biochemistry in an introductory course or textbook. Fortunately, the increased scope of knowledge allows scientists to make generalizations connecting the biochemical properties of living systems with the character of their constituent molecules. As a consequence, these generalizations, validated by repetitive examples, emerge in time as principles of biochemistry, principles that are useful in discerning and describing new relationships between diverse biomolecular functions and in predicting the mechanisms underlying newly discovered biomolecular processes. Nevertheless, it is increasingly apparent that students must develop skills in inquiry-based learning, so that, beyond this first encounter with biochemical principles and concepts, students are equipped to explore science on their own. Much of the design of this new edition is meant to foster the development of such skills.

We are both biochemists, but one of us is in a biology department, and the other is in a chemistry department. Undoubtedly, we each view biochemistry through the lens of our respective disciplines. We believe, however, that our collaboration on this textbook represents a melding of our perspectives that will provide new dimensions of appreciation and understanding for all students.

## Our Audience

This biochemistry textbook is designed to communicate the fundamental principles governing the structure, function, and interactions of biological molecules to students encountering biochemistry for the first time. We aim to bring an appreciation of

biochemistry to a broad audience that includes undergraduates majoring in the life sciences, physical sciences, or premedical programs, as well as medical students and graduate students in the various health sciences for whom biochemistry is an important route to understanding human physiology. To make this subject matter more relevant and interesting to all readers, we emphasize, where appropriate, the biochemistry of humans.

## Objectives and Building on Previous Editions

We carry forward the clarity of purpose found in previous editions; namely, to illuminate for students the principles governing the structure, function, and interactions of biological molecules. At the same time, this new edition has been revised to reflect tremendous developments in biochemistry. Significantly, emphasis is placed on the interrelationships of ideas so that students can begin to appreciate the overarching questions of biochemistry.

## Features

- **Clarity of Instruction** This edition was re-organized for increased clarity and readability. Many of the lengthier figure legends were shortened and more information was included directly within illustrations. These changes will help the more visual reader.
- **Visual Instruction** The richness of the Protein Data Bank (**www.pdb.org**) and availability of molecular graphics software has been exploited to enliven this text. Over 440 images of prominent proteins and nucleic acids involved with essential biological functions illustrate and inform the subject matter and were prepared especially for this book.
- **Essential Questions organization** Each chapter in this book is framed around an *Essential Question* that invites students to become actively engaged in their learning and encourages curiosity and imagination about the subject matter. For example, the Essential Question of Chapter 3 asks, "What are the laws and principles of thermodynamics that allow us to describe the flows and interchanges of heat, energy, and matter in biochemical systems?" The section heads then pose *Key Questions* that serve as organizing principles for a lecture such as, "What is the daily human requirement for ATP?" The subheadings are designed to be concept statements that respond to the section headings. The end-of-chapter *Summary* then brings each question together with a synopsis of the answer that summarizes the important concepts and facts to aid students in organizing and understanding the material.
- **Foundational Biochemistry** At the end of each chapter, a new Foundational Biochemistry feature has been added. These sections provide a comprehensive list of the principal facts and concepts that a student should understand after reading each chapter. Presented as short statements or descriptive phrases, the items of the Foundational Biochemistry list serve as guides to students of the knowledge they have acquired from the chapter and as checklists the students can review in assessing their learning.
- **End-of-Chapter Problems** More than 600 end-of-chapter problems are provided. They serve as meaningful exercises that help students develop problem-solving skills useful in achieving their learning goals. Some problems require students to employ calculations to find mathematical answers to relevant structural or functional questions. Other questions address conceptual problems whose answers require application and integration of ideas and concepts introduced in the chapter. Each set of problems includes MCAT practice questions to aid students in their preparation for standardized examinations such as the MCAT or GRE.
- **End-of-chapter problem headings** allow students to place the problem within the context of the subject matter they have learned.
- **Further Readings** sections at the end of each chapter make it easy for students to find up-to-date additional information about each topic.

- **Critical Developments in Biochemistry** essays emphasize recent and historical advances in the field.
- **Human Biochemistry** essays emphasize the central role of basic biochemistry in medicine and the health sciences. These essays often present clinically important issues such as diet, diabetes, and cardiovascular health.
- **A Deeper Look** essays expand on the text, highlighting selected topics or experimental observations.
- **Laboratory Techniques** The experimental nature of biochemistry is highlighted, and a list of laboratory techniques found in this book can be seen on page xxx.

## Highlights of This Edition

- **ActiveModels Library of Proteins and Nucleic Acids** is an optional online resource (**http://www.psafe.us**) for exploration of over 1,000 protein and nucleic acid structures, particularly those described in this text. Each structure is presented as a "Molecular Document" using the ICM Browser Pro modeling program developed by Molsoft, LLC in La Jolla, CA. These molecular documents were created by undergraduate biochemistry students at the University of Virginia and illustrate macromolecular structures with rich, vivid, state-of-the-art graphics accompanied by a script that highlights pertinent structure-function correlations. Hyperlinks in the text window of each entry control the graphic display and present a variety of perspectives and features for each protein or nucleic acid. A number of end-of-chapter problems challenge students to explore macromolecular structure and function through examination of these molecular documents.

### Recent Advances Highlighted in These Chapters

**Chapter 1** The foundations of biochemistry. New highlight: The eukaryotic cell likely emerged from an archaeal lineage. Contemporary eukaryotic cells are composites that harbor bacterial and archaeal contributions. A new Critical Developments in Biochemistry feature on synthetic life: the chemical synthesis of a bacterial genome and its incorporation into host cells to create the first organism with a fully synthetic genome.

**Chapter 2** This chapter reviews the properties of water, the nature of hydrophobic interactions, ionic equilibria, the behavior of weak acids, the concept of pH, and the major buffer systems in organisms.

**Chapter 3** This chapter features a simplified, more student-accessible presentation of the basic concepts of thermodynamics, highlighted by a new "A Deeper Look" box stressing the difference between free energy changes under cellular conditions, standard-state free energy changes ($\Delta G^\circ$), and the situation at equilibrium ($\Delta G = 0$).

**Chapter 4** The structure and chemistry of amino acids. An introduction to the Brainbow technique that enables labeling of many individual neurons. New A Deeper Look box on the unusual amino acid selenocysteine and selenoproteins, and a new Critical Developments in Biochemistry box on incorporation of unnatural amino acids into proteins.

**Chapter 5** Proteins as polymers of amino acids; proteins as macromolecules of elaborate structure; proteins as the agents of biological function. A new section defining the concept of the proteome and what new insights emerge from such large-scale, global studies of all the proteins in a given cell or tissue. The proteome is an excellent reflection of what a particular cell is doing at a specific moment in time.

**Chapter 6** The higher-order structure of proteins. A Deeper Look feature on protein sectors—evolutionary units of three-dimensional structure, and a new Deeper Look feature on metamorphic proteins, which exist as an ensemble of structures of similar energies and stabilities. A new "Human Biochemistry" box on chimeric antigen receptor (CAR) T-cell therapies as the basis of novel cancer treatments, and a new "A Deeper Look" box on friction in the protein folding process, as well as expanded coverage of intrinsically disordered proteins.

**Chapter 7** The structure and chemistry of carbohydrates. The discovery that the disaccharide galactose-$\alpha$-1,3-galactose ("alpha gal") triggers red meat allergy. A new "A Deeper Look" box on the chemistry of cellulose crosslinks in wrinkle-free fabrics, and a new "A Deeper Look" box on the role of N-linked oligosaccharides in protein folding.

**Chapter 8** The structure and chemistry of lipids. A new Deeper Look feature on glycophospholipids that play a role in formation of plasma membrane signaling microdomains involved in cellular differentiation and maturation. Also a new Human Biochemistry feature on the endocannabinoid signaling system that involves lipid-soluble signals such as anandamide and 2-arachidonoylglycerol. The signaling effects of sphingosine-1-phosphate.

**Chapter 9** Membrane structure and function. A new Human Biochemistry feature on development of inhibitors of *N*-myristoyltransferase in *T. brucei*, the organism that causes sleeping sickness in Africa. Also revised discussions of the roles of sphingolipid and cholesterol in the formation of membrane rafts and the structures and functions of SNARE proteins and channel proteins. Five new end-of-chapter problems based on recent research on membrane proteins and transport sytems.

**Chapter 10** The structure and chemistry of nucleotides and nucleic acids. New appreciation of cyclic dinucleotides as signaling molecules, including the role of cGAMP in triggering a program of gene expression aimed at halting infection. An updated introduction to the many roles of small RNAs in the regulation of gene expression: miRNAs and the long, noncoding RNAs (lincRNAs).

**Chapter 11** The structure of nucleic acids and chromosomes. An overview of the next-generation DNA sequencing technologies, including emerging technologies to sequence single molecules of DNA. The techniques at the forefront of "personal genomics": the ability to carry out low-cost sequencing of an individual's genome and the implications of the information obtained on the diagnosis and treatment of disease. Also, creation of DNA molecules composed of not just two, but three, different base pairs opens up extraordinary potentials within synthetic biology. New structural models for chromatin at the level of its 30-nm fiber 'secondary structure' give insights into the long mysterious higher-order structure of chromosomes. A discussion of how new biological roles of RNA have come into sharper focus because of recent realizations that their three-dimensional architectures are conformationally dynamic, endowing these RNAs with functional abilities, such as ligand binding and even catalysis.

**Chapter 12** The strategies of recombinant DNA technology and gene cloning. New features include a section devoted to high-throughput technologies that allow global study of millions of genes or proteins in a single experiment and a section devoted to the emerging field of synthetic biology, with special emphasis on the use of CRISPR/Cas9 to edit genes and genomes.

**Chapter 13** The equations of enzyme kinetics. A new perspective on the response of enzyme reaction rate to increasing temperature is presented, wherein a temperature-dependent equilibrium between active enzyme and a catalytically inactive but not denatured state of the enzyme affords a deeper understanding of enzyme kinetics. Ribozymes, abzymes, and designer enzymes are featured here.

**Chapter 14** Mechanisms of enzyme action. A new section on the role of quantum mechanical tunneling in electron and proton transfer reactions of enzymes. New Human Biochemistry box on antibiotic resistance by (carbapenem-resistant) superbugs. New Critical Developments in Biochemistry box on acceleration of enzyme reactions by electric fields.

**Chapter 15** Enzyme regulation. This chapter highlights allosteric regulation and covalent modification of enzymes as important modes of metabolic regulation and includes discussion of reversible acetylation, a newly appreciated means to regulate metabolic enzymes. The relationship between quaternary structure and allosteric regulation is exemplified by a comparison of the oxygen-binding proteins myoglobin and hemoglobin.

**Chapter 16** Motor proteins. A revised discussion of P-loop NTPases and their role in molecular motors and a revised section on the contraction cycle of skeletal muscle. New Human Biochemistry box on the "tubulin code" post-translational modifications that coordinate the functions of microtubules.

**Chapter 17** An overview of metabolism, to prepare students for the ten chapters on metabolic pathways which follow. This edition highlights metabolomics, the study of all the metabolites in a cell at a particular moment, as the most accurate representation of what a cell is doing at any instant.

**Chapter 18** Glycolysis. A Critical Developments in Biochemistry feature that describes a modern interpretation of the Warburg effect in cancer. Expanded coverage of glucokinase and its role as a glucose sensor that recognizes glucose and initiates a signaling pathway that results in glucose-induced insulin secretion. New information on protein kinase M2 (PK M2), including its newly-discovered protein kinase activity, its stimulation by SAICAR (an intermediate in the purine biosynthetic pathway), and its role in tumor proliferation. New coverage of the unregulated metabolism of dietary fructose in the liver, and its implications for insulin resistance, metabolic syndrome, and obesity.

**Chapter 19** The citric acid cycle. A new discussion of the structure of pyruvate dehydrogenase comple; a new Deeper Look feature on the role of anaplerosis in insulin secretion; and a section on the regulation of TCA cycle enzymes by acetylation. A new Human Biochemistry box on the roles of citric acid cycle metabolites in post-translational modification of proteins, including acetylation, succinylation, and succination reactions. New information on the operation of the eight citric cycle enzymes as a supercomplex or metabolon.

**Chapter 20** Electron transport and oxidative phosphorylation. Discussion of the new structure of Complex I and new information on supercomplexes in electron transport. New insights into the mechanism of action of the $F_1F_0$-ATP synthase. A new Human Biochemistry box describing mitochondrial dynamics and its role in cardiovascular, neurodegenerative, and endocrine diseases, as well as cancer. A new Human Biochemistry box on cardiolipin and its stabilization of respiratory supercomplexes, the biogenesis of mitochondrial proteins, and the fission and fusion processes of mitochondria.

**Chapter 21** Photosynthesis—the most fundamental of all energy transduction systems in nature: the biochemistry of photosynthesis; the transformation of light energy into chemical energy. New information on species variability in the c-subunit stoichiometry of $CF_1CF_0$-ATP synthases and the implications of this variability for the energetic cost of ATP formation. The recently described structure of the $Mn_4CaO_5$ oxygen-evolving cluster at the heart of Photosystem II is presented. Emphasis on the pathway of carbon dioxide fixation that synthesizes organic molecules from $CO_2$, ultimately leading to cellulose and starch formation, the two significant polysaccharides produced by plants.

**Chapter 22** Gluconeogenesis, glycogen metabolism, and the pentose phosphate pathway. A Deeper Look feature on TIGAR, a p53-induced enzyme that mimics fructose-2,6-bisphosphatase and responds to cellular stresses such as oncogenesis and DNA damage events; new information on O-GlcNAc signaling and the hexosamine biosynthetic pathway; and a new Critical Developments in Biochemistry feature describing how consumption of ATP promotes and supports the metabolism of cancer cells. The interplay of phosphorylation and O-GlcNAcylation in gluconeogenic gene transcription, particularly in the fasting state.

**Chapter 23** Fatty acid oxidation. A new Deeper Look feature on the biochemistry of obesity describing the role of peroxisome proliferator-activated receptors in regulation of gene expression in

fatty acid oxidation and triglyceride metabolism. A new A Deeper Look box describing the trifunctional enzyme complex at the heart of the $\beta$-oxidation pathway and migration of its fatty acyl substrates along a negatively-charged substrate channel without diffusing into the bulk solvent. The role of $\beta$-hydroxybutyrate as a signaling metabolite that regulates gene expression, lipid metabolism, metabolic rate, and resistance to oxidative stress.

**Chapter 24** Lipid biosynthesis. A Human Biochemistry box featuring the role of NPC1 and NPC2 proteins in cholesterol transport in lysosomes and Niemann-Pick type C disease. Four new Human Biochemistry boxes: Lipins—phosphatases essential for triglyceride synthesis and other functions; Lipoxins—anti-inflammatory eicosanoid products of transcellular metabolism; APOC3—an apolipoprotein that regulates plasma triglyceride levels; and new cholesterol-lowering drugs that target PCSK9, an LDL receptor chaperone.

**Chapter 25** The assimilation of inorganic nitrogen into organic nitrogen metabolites and biosynthesis of the amino acids. Discussion of glutamine and its metabolic significance as the most abundant amino acid in human body fluids and tissues; glutamine and cancer. Further, tryptophan catabolism by the kynurenine pathway is presented, because this pathway has been implicated in human neurodegenerative disorders such as Parkinson's and Alzheimer's disease.

**Chapter 26** Biosynthesis of purines and pyrimidines. Tetrahydrofolate and 1-carbon metabolism. Purinosomes as multi-enzyme assemblages of the purine biosynthetic enzymes. The purine pathway intermediate SAICAR as a key signal in reprogramming metabolism in cancer cells. The structure of human ribonucleotide reductase with its revelations regarding regulation by nucleotides are presented.

**Chapter 27** Summing up metabolism and the metabolic roles of the various organs. AMP-kinase (AMPK) as the cell's energy charge sensor and the newly appreciated protection of AMPK by ADP are discussed. mTORC1 as the integrator of information about nutrient status and as the regulator of cellular synthesis is introduced. The regulation of eating behavior. The relationships between nutrient intake, AMPK, SIRT1 and protein acetylation and the consequences that these relationships have for caloric intake control and the development of metabolic syndrome. These interactions illuminate the underlying causes of the current obesity epidemic.

**Chapter 28** DNA metabolism. The multiplicity of DNA polymerases. A new section to integrate DNA replication, recombination, and repair as interdependent aspects of DNA metabolism introduces this chapter. Another new feature is an illustration of how homologous recombination helps to prevent cancer. Genetic recombination, protein diversity, and immunology.

**Chapter 29** Transcription; DNA-dependent RNA polymerases. Transcription regulation in bacteria and in eukaryotes, An update of eukaryotic translation initiation events in eukaryotes and the emerging science of miRNAs and lncRNAs as key regulators of post-transcriptional gene expression are presented, along with new structural and functional information about Mediator and its role as a bridge between enhancers of transcription and RNA polymerase II. The competing concepts of the histone code and histone crosstalk are discussed. The spliceosome.

**Chapter 30** Protein synthesis. The genetic code. Aminoacyl-tRNA synthetases and the second genetic code. New features of the G-protein family members, Ef-Tu and EF-G, and their interactions with the ribosome, new structures for the ribosome RF-2 termination complex, and the more richly detailed appreciation of the events in eukaryotic translation initiation highlight this chapter. The ribosome as a ribozyme. Tethered ribosomes and new frontiers in synthetic biology.

**Chapter 31** Completing the protein life cycle. Modes of post-transcriptional modification that control the functional protein pool, Protein folding and neurodegenerative protein folding diseases. A new Human Biochemistry box on chaperones that function by stress-induced protein unfolding. A Human Biochemistry highlight on autophagy, the process by which cells recycle their materials. Expanded coverage of Htr proteins.

**Chapter 32** Cell signaling and neurotransmission. Intracellular responses to extracellular signals. Protein kinase cascades. Organization and integration of signaling pathways. Sensory systems. A Human Biochemistry feature on neurexins and neuroligins, which function as scaffolding proteins in the formation of synapses and the regulation of synaptic transmission, learning, and memory.

## Supporting Materials

### For the Instructor

Please visit **http://www.cengage.com/chemistry/garrett/biochem6e** for more information about instructor resources for this text.

### For the Student

Please visit **http://www.cengage.com/chemistry/garrett/biochem6e** for more information about student resources for this text.

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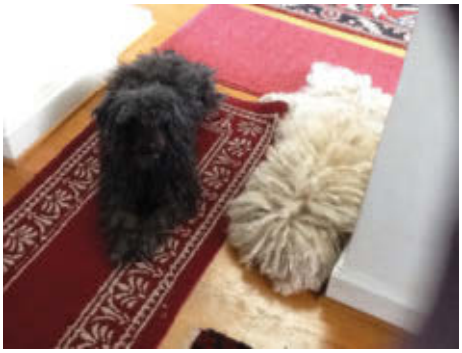
Jazmine and Jatszi


Clancy


Jax and Jasper

"Imagination is more important than knowledge. For while knowledge defines all we currently know and understand, imagination points to all we might yet discover and create."
*—Albert Einstein*

Reginald H. Garrett
*Charlottesville, VA*

Charles M. Grisham
*Ivy, VA*

*November, 2015*

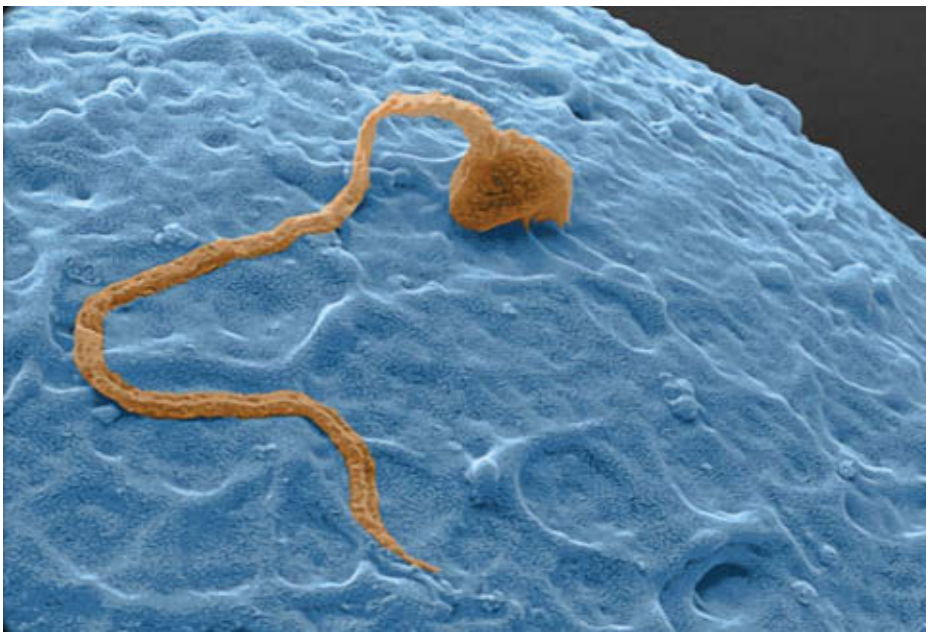
# The Facts of Life: Chemistry Is the Logic of Biological Phenomena

1

PART I
MOLECULAR COMPONENTS OF CELLS

*"…everything that living things do can be understood in terms of the jigglings and wigglings of atoms."*

*Richard P. Feynman. Lectures on Physics,* Addison-Wesley, 1963



Marmaduke St. John/Alamy

◀ Sperm fertilizing an egg.

## ESSENTIAL QUESTION

Molecules are lifeless. Yet, the properties of living things derive from the properties of molecules. **Despite the spectacular diversity of life, the elaborate structure of biological molecules, and the complexity of vital mechanisms, are life functions ultimately interpretable in chemical terms?**

## KEY QUESTIONS



Molecules are lifeless. Yet, in appropriate complexity and number, molecules compose living things. These living systems are distinct from the inanimate world because they have certain extraordinary properties. They can grow, move, perform the incredible chemistry of metabolism, respond to stimuli from the environment, and, most significantly, replicate themselves with exceptional fidelity. The complex structure and behavior of living organisms veil the basic truth that their molecular constitution can be described and understood. The chemistry of the living cell resembles the chemistry of organic reactions. Indeed, cellular constituents, or **biomolecules**, must conform to the chemical and physical principles that govern all matter. Despite the spectacular diversity of life, the intricacy of biological structures, and the complexity of vital mechanisms, life functions are ultimately interpretable in chemical terms. *Chemistry is the logic of biological phenomena. Living organisms are self-sustaining systems of chemical reactions.*

## 1.1 What Are the Distinctive Properties of Living Systems?

First, the most obvious quality of **living organisms** is that they are *complicated and highly organized* (Figure 1.1). For example, organisms large enough to be seen with the naked eye are composed of many **cells**, typically of many types. In turn, these cells possess subcellular structures, called **organelles**, which are complex assemblies of very large


(a)


(b)

FIGURE 1.1 **(a)** Gelada *(Theropithecus gelada)*, a baboon native to the Ethiopian highlands. **(b)** Tropical orchid *(Masdevallia norops)*, Ecuador.

polymeric molecules, called **macromolecules**. These macromolecules themselves show an exquisite degree of organization in their intricate three-dimensional architecture, even though they are composed of simple sets of chemical building blocks, such as sugars and amino acids. Indeed, the complex three-dimensional structure of a macromolecule, known as its **conformation**, is a consequence of interactions between the monomeric units, according to their individual chemical properties.

Second, *biological structures serve functional purposes*. That is, biological structures play a role in the organism's existence. From parts of organisms, such as limbs and organs, down to the chemical agents of metabolism, such as enzymes and metabolic intermediates, a biological purpose can be given for each component. Indeed, it is this functional characteristic of biological structures that separates the science of biology from studies of the inanimate world such as chemistry, physics, and geology. In biology, it is always meaningful to seek the purpose of observed structures, organizations, or patterns; that is, to ask what functional role they serve within the organism.

Third, *living systems are actively engaged in energy transformations*. Maintenance of the highly organized structure and activity of living systems depends on their ability to extract energy from the environment. The ultimate source of energy is the sun. Solar energy flows from photosynthetic organisms (organisms able to capture light energy by the process of photosynthesis) through food chains to herbivores and ultimately to carnivorous predators at the apex of the food pyramid (Figure 1.2). The biosphere is thus a system through which energy flows. Organisms capture some of this energy, be it from photosynthesis or the metabolism of food, by forming special energized biomolecules, of which **ATP** and **NADPH** are the two most prominent examples (Figure 1.3). (Commonly used abbreviations such as ATP and NADPH are defined on the inside back cover of this book.) ATP and NADPH are energized biomolecules because they represent chemically useful forms of stored energy. We explore the chemical basis of this stored energy in subsequent chapters. For now, suffice it to say that when these molecules react with other molecules in the cell, the energy released can be used to drive energetically unfavorable processes. That is, ATP, NADPH, and related compounds are the power sources that drive the energy-requiring activities of the cell, including biosynthesis, movement, osmotic work against concentration gradients, and, in special instances, light emission (bioluminescence). Only upon death does an organism reach equilibrium with its inanimate environment. *The living state is characterized by the flow of energy through the organism*. At the expense of this energy flow, the organism can maintain its intricate order and activity far removed from equilibrium with its surroundings, yet exist in a state of apparent constancy over time. This state of apparent constancy, or so-called **steady state**, is actually a very dynamic condition: Energy and

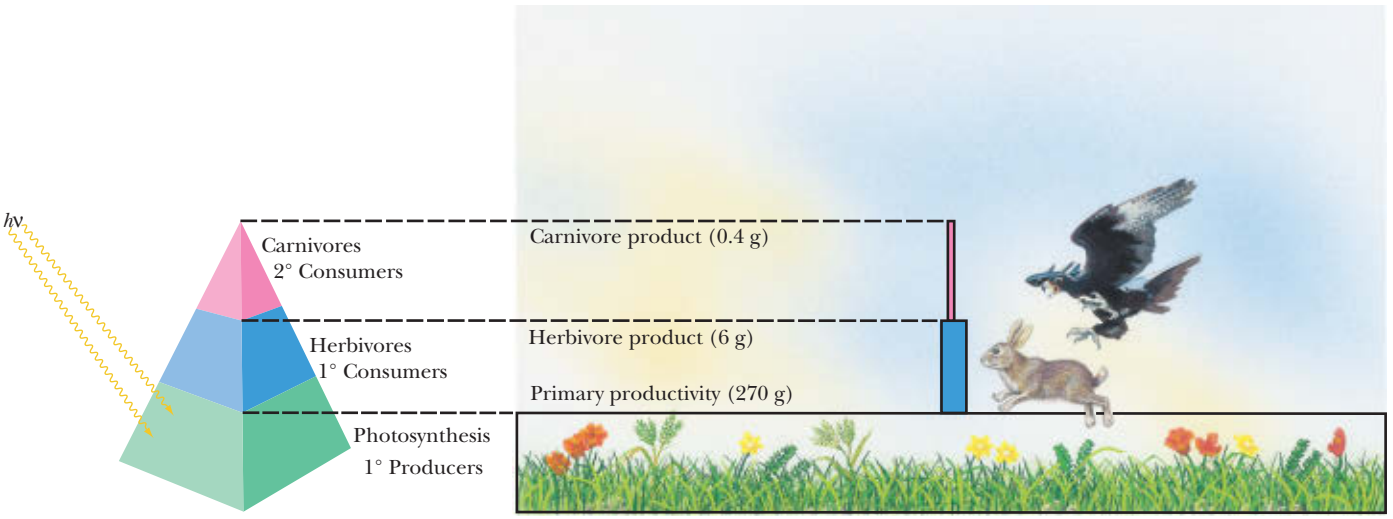



FIGURE 1.2 The food pyramid. Photosynthetic organisms at the base capture light energy. Herbivores and carnivores derive their energy ultimately from these primary producers.

material are consumed by the organism and used to maintain its stability and order. In contrast, inanimate matter, as exemplified by the universe in totality, is moving to a condition of increasing disorder or, in thermodynamic terms, maximum **entropy** ▸.

**Entropy** ▸ A thermodynamic term used to designate that amount of energy in a system that is unavailable to do work.

Fourth, *living systems have a remarkable capacity for self-replication*. Generation after generation, organisms reproduce virtually identical copies of themselves. This self-replication can proceed by a variety of mechanisms, ranging from simple division in bacteria to sexual reproduction in plants and animals; but in every case, it is characterized by an astounding degree of fidelity (Figure 1.4). Indeed, if the accuracy of self-replication were significantly greater, the evolution of organisms would be hampered. This is so because evolution depends upon natural selection operating on individual organisms that vary slightly in their fitness for the environment. The fidelity of self-replication resides ultimately in the chemical nature of the genetic material. This substance consists of polymeric chains of deoxyribonucleic acid, or **DNA**, which are structurally complementary to one another (Figure 1.5). These molecules can generate new copies of themselves in a rigorously

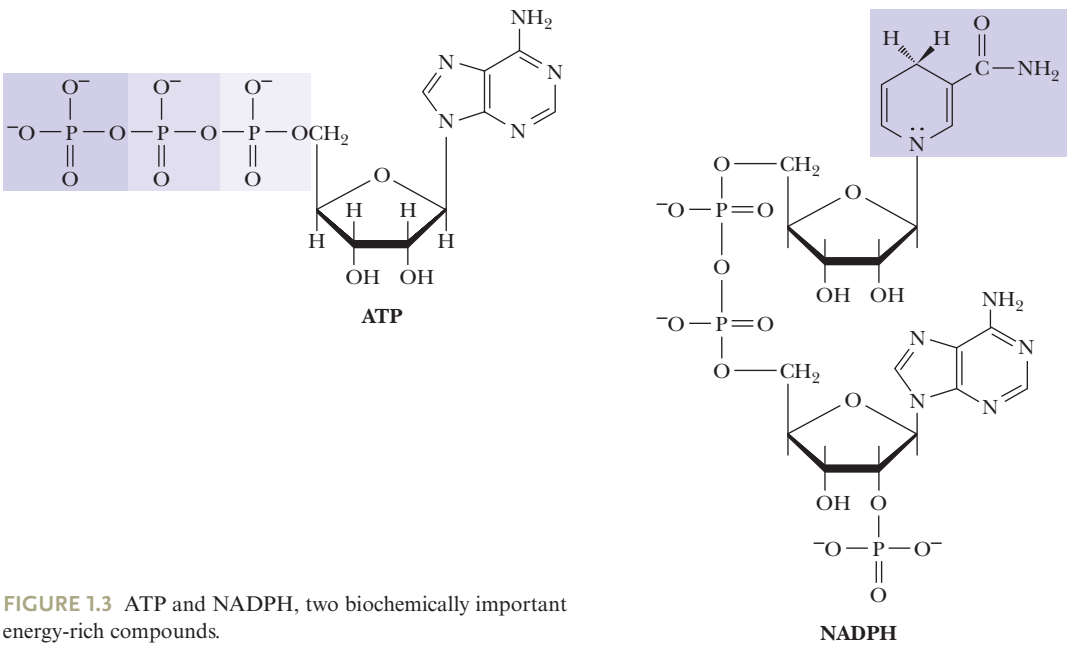
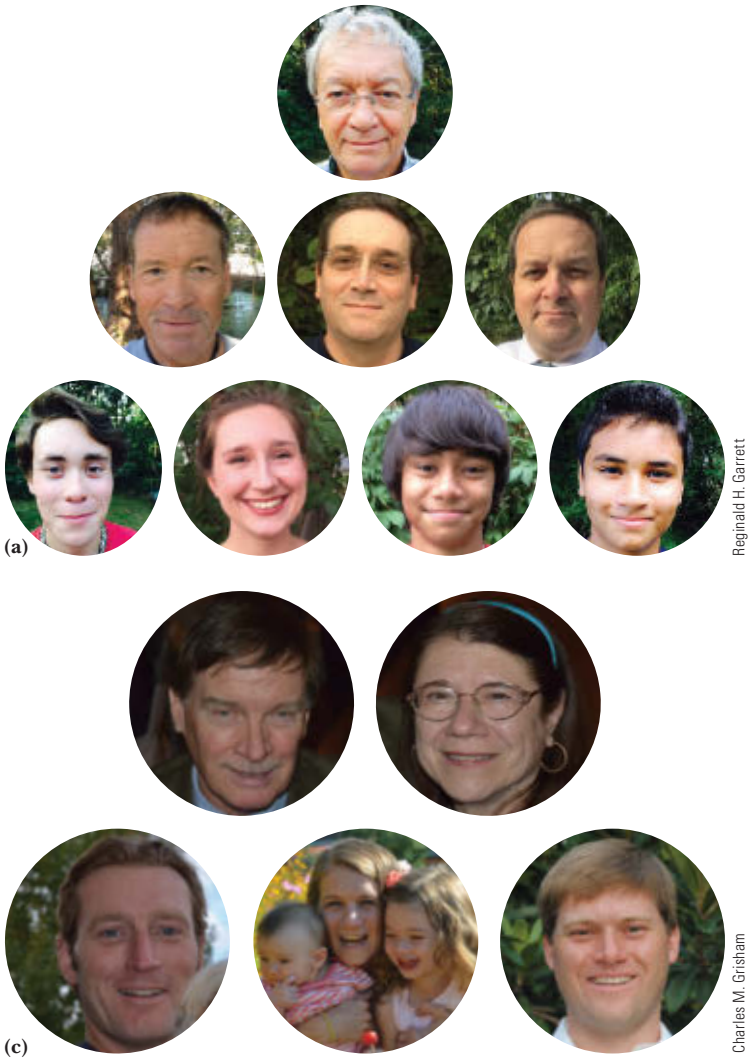



FIGURE 1.3 ATP and NADPH, two biochemically important energy-rich compounds.





(b)

**FIGURE 1.4** Organisms resemble their parents. **(a)** The Garrett lineage. Top-to-bottom, left-to-right: Reg Garrett; sons Jeffrey, Randal, and Robert; grandchildren Jackson, Bella, Reggie, and Ricky. **(b)** Orangutan with infant. **(c)** The Grisham family. Top-to-bottom, left-to-right: Charles and Rosemary; son David, daughter Emily with granddaughters Annie and May, son Andrew.

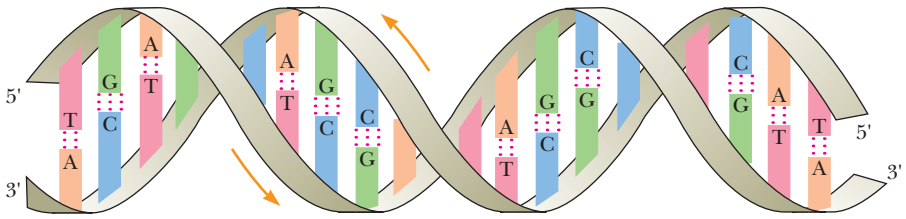



**FIGURE 1.5** The DNA double helix. Two complementary polynucleotide chains running in opposite directions can pair through hydrogen bonding between their nitrogenous bases. Their complementary nucleotide sequences give rise to structural complementarity.

executed polymerization process that ensures a faithful reproduction of the original DNA strands. In contrast, the molecules of the inanimate world lack this capacity to replicate. A crude mechanism of replication must have existed at life's origin.

## 1.2 | What Kinds of Molecules Are Biomolecules?

The elemental composition of living matter differs markedly from the relative abundance of elements in the earth's crust (Table 1.1). Hydrogen, oxygen, carbon, and nitrogen constitute more than 99% of the atoms in the human body, with most of the H and O occurring as $H_2O$. Oxygen, silicon, aluminum, and iron are the most abundant atoms in the earth's crust, with hydrogen, carbon, and nitrogen being relatively rare (less than

**TABLE 1.1 Composition of the Earth's Crust, Seawater, and the Human Body***

| Earth's Crust | | Seawater | | Human Body† | |
|---|---|---|---|---|---|
| Element | % | Compound | m*M* | Element | % |
| O | 47 | $Cl^-$ | 548 | H | 63 |
| Si | 28 | $Na^+$ | 470 | O | 25.5 |
| Al | 7.9 | $Mg^{2+}$ | 54 | C | 9.5 |
| Fe | 4.5 | $SO_4^{2-}$ | 28 | N | 1.4 |
| Ca | 3.5 | $Ca^{2+}$ | 10 | Ca | 0.31 |
| Na | 2.5 | $K^+$ | 10 | P | 0.22 |
| K | 2.5 | $HCO_3^-$ | 2.3 | Cl | 0.08 |
| Mg | 2.2 | $NO_3^-$ | 0.01 | K | 0.06 |
| Ti | 0.46 | $HPO_4^{2-}$ | <0.001 | S | 0.05 |
| H | 0.22 | | | Na | 0.03 |
| C | 0.19 | | | Mg | 0.01 |

*Figures for the earth's crust and the human body are presented as percentages of the total number of atoms; seawater data are in millimoles per liter. Figures for the earth's crust do not include water, whereas figures for the human body do.
†Trace elements found in the human body serving essential biological functions include Mn, Fe, Co, Cu, Zn, Mo, I, Ni, and Se.

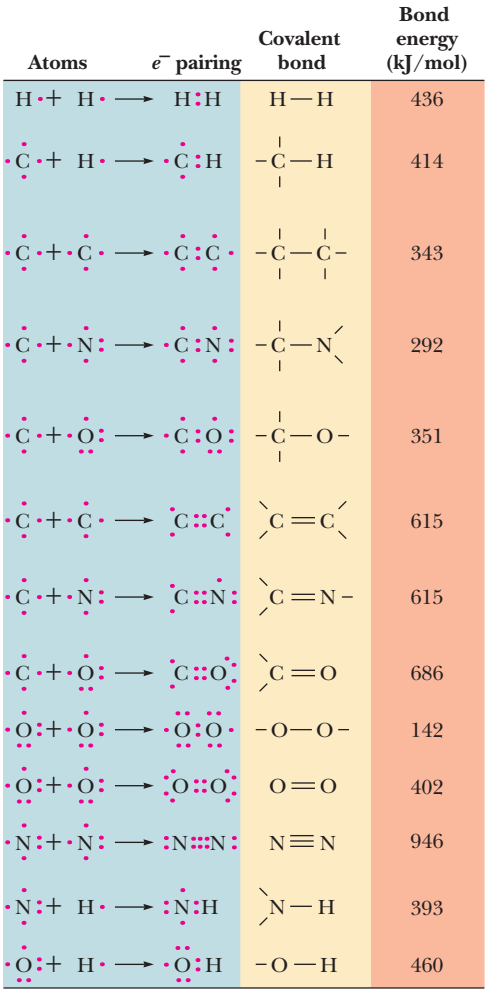



**FIGURE 1.6** Covalent bond formation by $e^-$ pair sharing.

0.2% each). Nitrogen as dinitrogen ($N_2$) is the predominant gas in the atmosphere, and carbon dioxide ($CO_2$) is present at a level of 0.04%, a small but critical amount. Oxygen is also abundant in the atmosphere and in the oceans. What property unites H, O, C, and N and renders these atoms so suitable to the chemistry of life? It is their ability to form covalent bonds by electron-pair sharing. Furthermore, H, C, N, and O are among the lightest elements of the periodic table capable of forming such bonds (Figure 1.6). Because the strength of covalent bonds is inversely proportional to the atomic weights of the atoms involved, H, C, N, and O form the strongest covalent bonds. Two other covalent bond-forming elements, phosphorus (as phosphate [$—OPO_3^{2-}$] derivatives) and sulfur, also play important roles in biomolecules.

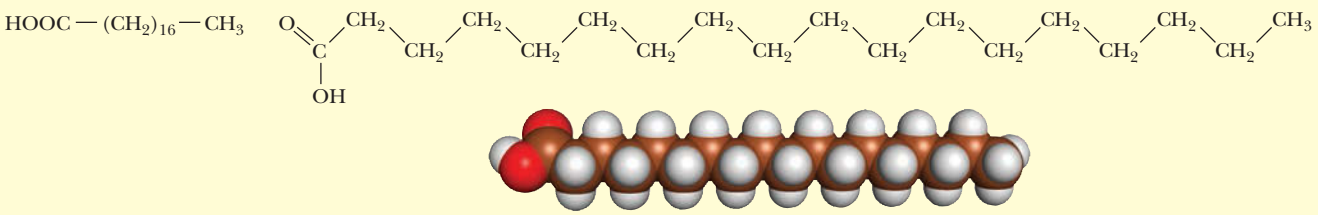
## 1.2a Biomolecules Are Carbon Compounds

All biomolecules contain carbon (C). The prevalence of C is due to its unparalleled versatility in forming stable covalent bonds through electron-pair sharing. Carbon can form as many as four such bonds by sharing each of the four electrons in its outer shell with electrons contributed by other atoms. Atoms commonly found in covalent linkage to C are C itself, H, O, and N. Hydrogen can form one such bond by contributing its single electron to the formation of an electron pair. Oxygen, with two unpaired electrons in its outer shell, can participate in two covalent bonds, and nitrogen, which has three unshared electrons, can form three such covalent bonds. Furthermore, C, N, and O can share two electron pairs to form double bonds with one another within biomolecules, a property that enhances their chemical versatility. Carbon and nitrogen can even share three electron pairs to form triple bonds.

Two properties of carbon covalent bonds merit particular attention. One is the ability of carbon to form covalent bonds with itself. The other is the tetrahedral nature of the four covalent bonds when carbon atoms form only single bonds. Together these properties hold the potential for an incredible variety of linear, branched, and cyclic compounds of C. This diversity is multiplied further by the possibilities for including N, O, and H atoms in these compounds (Figure 1.7). We can therefore envision the ability of C to generate complex structures in three dimensions. These structures, by virtue of appropriately included N, O, and H atoms, can display unique chemistries suitable to the living state. Thus, we may ask, is there any pattern or underlying organization that brings order to this astounding potentiality?

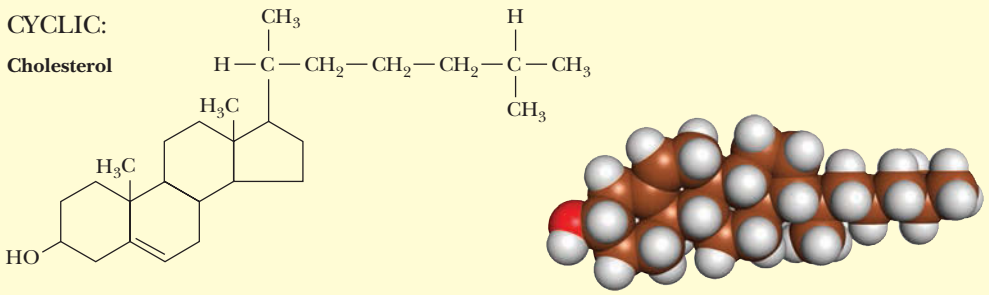
LINEAR ALIPHATIC:

**Stearic acid**



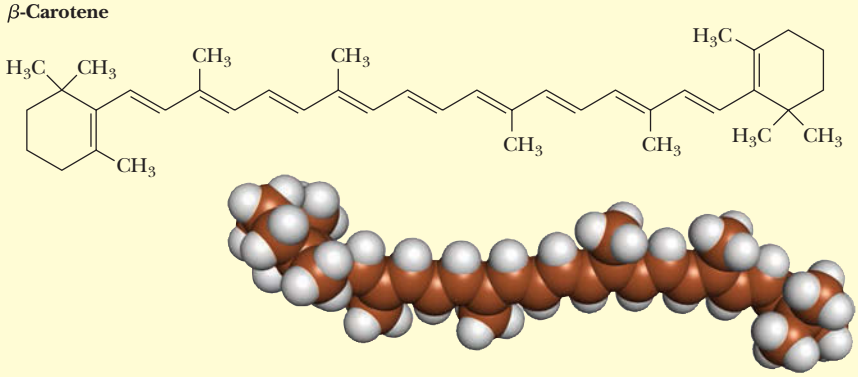
CYCLIC:

**Cholesterol**



BRANCHED:

***β*-Carotene**



PLANAR:

**Chlorophyll *a***

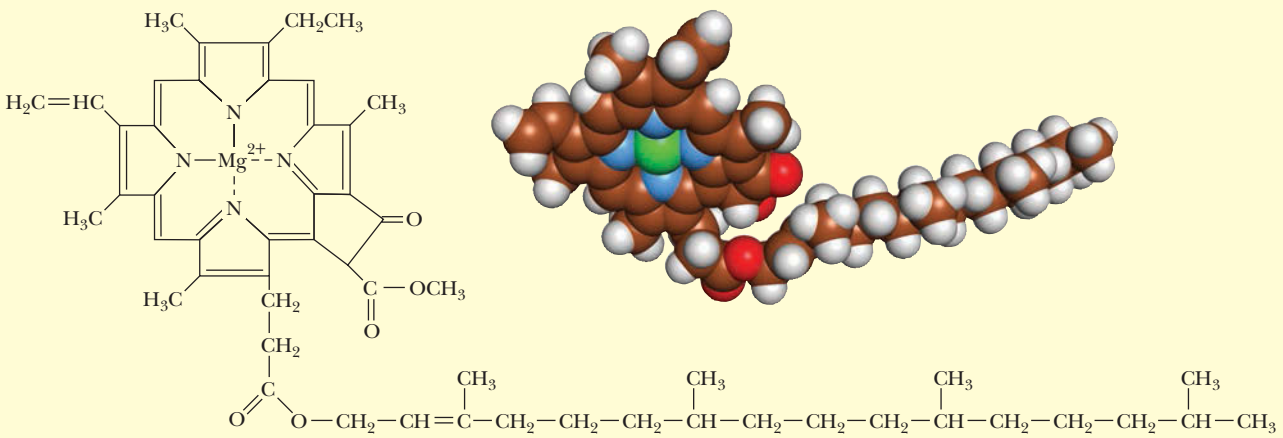


FIGURE 1.7 Examples of the versatility of C—C bonds in building complex structures: linear, cyclic, branched, and planar.

## 1.3 What Is the Structural Organization of Complex Biomolecules?

Examination of the chemical composition of cells reveals a dazzling variety of organic compounds covering a wide range of molecular dimensions (Table 1.2). As this complexity is sorted out and biomolecules are classified according to the similarities of their sizes and chemical properties, an organizational pattern emerges. The biomolecules are built according to a structural hierarchy: Simple molecules are the units for building complex structures.

The molecular constituents of living matter do not reflect randomly the infinite possibilities for combining C, H, O, and N atoms. Instead, only a limited set of the many possibilities is found, and these collections share certain properties essential to the establishment and maintenance of the living state. The most prominent aspect of biomolecular organization is that macromolecular structures are constructed from simple molecules according to a hierarchy of increasing structural complexity. What properties do these biomolecules possess that make them so appropriate for the condition of life?

### 1.3a Metabolites Are Used to Form the Building Blocks of Macromolecules

The major precursors for the formation of biomolecules are water, carbon dioxide, and three inorganic nitrogen compounds—ammonium ($NH_4^+$), nitrate ($NO_3^-$), and dinitrogen ($N_2$). Metabolic processes assimilate and transform these inorganic precursors through ever more complex levels of biomolecular order (Figure 1.8). In the first step,

**TABLE 1.2 Biomolecular Dimensions**

The dimensions of mass* and length for biomolecules are given typically in daltons and nanometers,† respectively. One dalton (D) is approximately equal to the mass of one hydrogen atom, $1.66 \times 10^{-24}$ g. One nanometer (nm) is $10^{-9}$ m, or 10 Å (angstroms).

| | | Mass | |
|---|---|---|---|
| Biomolecule | Length (long dimension, nm) | Daltons | Picograms |
| Water | 0.3 | 18 | |
| Alanine | 0.5 | 89 | |
| Glucose | 0.7 | 180 | |
| Phospholipid | 3.5 | 750 | |
| Ribonuclease (a small protein) | 4 | 12,600 | |
| Immunoglobulin G (IgG) | 14 | 150,000 | |
| Myosin (a large muscle protein) | 160 | 470,000 | |
| Ribosome (bacteria) | 18 | 2,520,000 | |
| Bacteriophage $\phi$X174 (a very small bacterial virus) | 25 | 4,700,000 | |
| Pyruvate dehydrogenase complex (a multienzyme complex) | 60 | 7,000,000 | |
| Tobacco mosaic virus (a plant virus) | 300 | 40,000,000 | $6.68 \times 10^{-5}$ |
| Mitochondrion (liver) | 1,500 | | 1.5 |
| *Escherichia coli* cell | 2,000 | | 2 |
| Chloroplast (spinach leaf) | 8,000 | | 60 |
| Liver cell | 20,000 | | 8,000 |

*Molecular mass is expressed in units of daltons (D) or kilodaltons (kD) in this book; alternatively, the dimensionless term *molecular weight*, symbolized by $M_r$, and defined as the ratio of the mass of a molecule to 1 dalton of mass, is used.

†Prefixes used for powers of 10 are

| | | | | | |
|---|---|---|---|---|---|
| $10^6$ | mega | M | $10^{-3}$ | milli | m |
| $10^3$ | kilo | k | $10^{-6}$ | micro | $\mu$ |
| $10^{-1}$ | deci | d | $10^{-9}$ | nano | n |
| $10^{-2}$ | centi | c | $10^{-12}$ | pico | p |
| | | | $10^{-15}$ | femto | f |

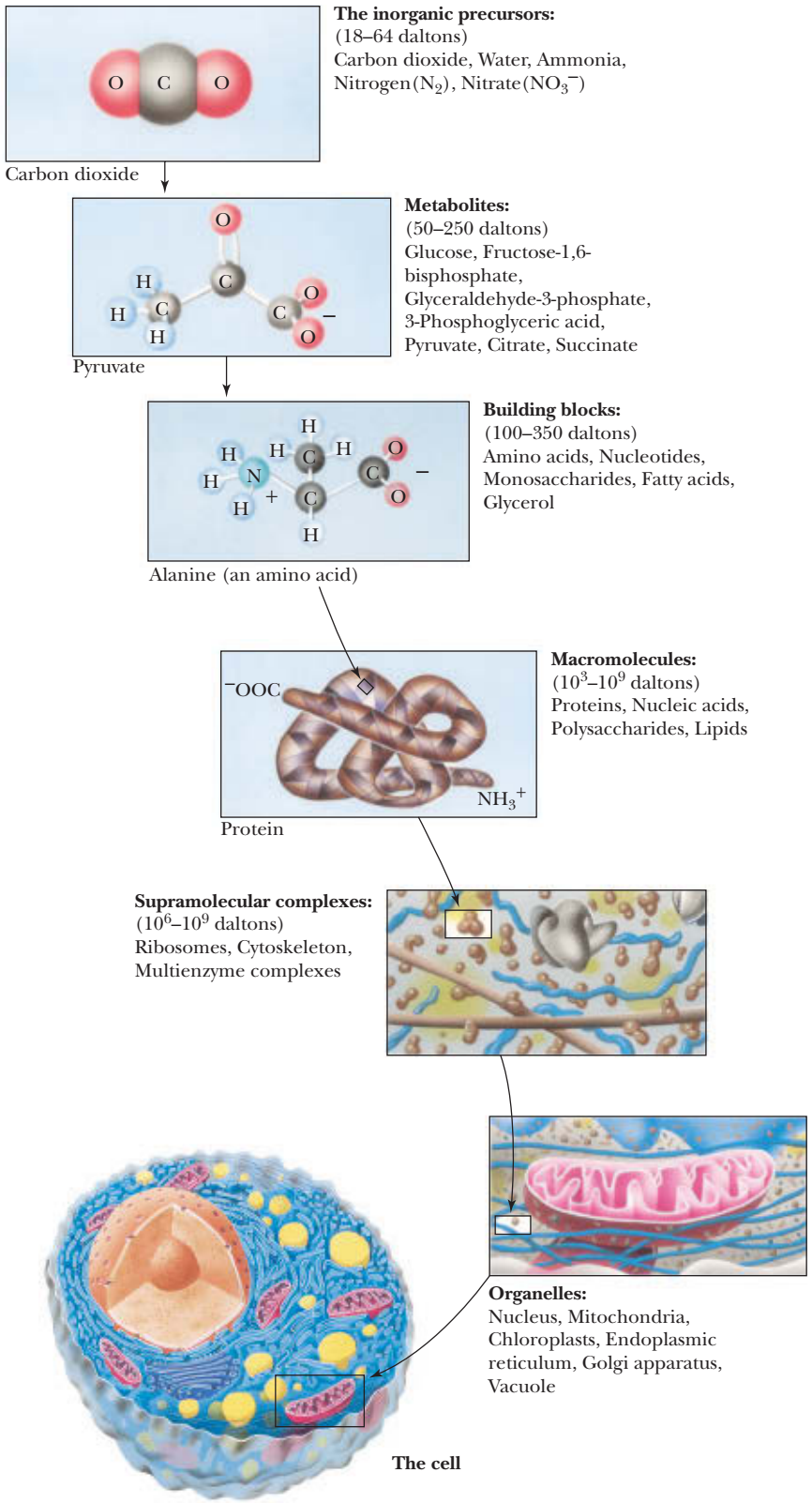



FIGURE 1.8 Molecular organization in the cell is a hierarchy.

precursors are converted to **metabolites**, simple organic compounds that are intermediates in cellular energy transformation and in the biosynthesis of various sets of **building blocks**: amino acids, sugars, nucleotides, fatty acids, and glycerol. Through covalent linkage of these building blocks, the **macromolecules** are constructed: proteins, polysaccharides, polynucleotides (DNA and RNA), and lipids. (Strictly speaking, lipids

contain relatively few building blocks and are therefore not really polymeric like other macromolecules; however, lipids are important contributors to higher levels of complexity.) Interactions among macromolecules lead to the next level of structural organization, **supramolecular complexes**. Here, various members of one or more of the classes of macromolecules come together to form specific assemblies that serve important subcellular functions. Examples of these supramolecular assemblies are multifunctional enzyme complexes, ribosomes, chromosomes, and cytoskeletal elements. For example, a eukaryotic ribosome contains four different RNA molecules and at least 70 unique proteins. These supramolecular assemblies are an interesting contrast to their components because their structural integrity is maintained by noncovalent forces, not by covalent bonds. These noncovalent forces include hydrogen bonds, ionic attractions, van der Waals forces, and hydrophobic interactions between macromolecules. Such forces maintain these supramolecular assemblies in a highly ordered functional state. Although noncovalent forces are weak (less than 40 kJ/mol), they are numerous in these assemblies and thus can collectively maintain the essential architecture of the supramolecular complex under conditions of temperature, pH, and ionic strength that are consistent with cell life.

### 1.3b Organelles Represent a Higher Order in Biomolecular Organization

The next higher rung in the hierarchical ladder is occupied by the organelles, entities of considerable dimensions compared with the cell itself. Organelles are found only in **eukaryotic cells**, that is, the cells of "higher" organisms (eukaryotic cells are described in Section 1.5). Several kinds, such as mitochondria and chloroplasts, evolved from bacteria that gained entry to the cytoplasm of early eukaryotic cells. Organelles share two attributes: They are cellular inclusions, usually membrane bounded; and they are dedicated to important cellular tasks. Organelles include the nucleus, mitochondria, chloroplasts, endoplasmic reticulum, Golgi apparatus, and vacuoles, as well as other relatively small cellular inclusions, such as peroxisomes, lysosomes, and chromoplasts. The **nucleus** is the repository of genetic information as contained within the linear sequences of nucleotides in the DNA of chromosomes. **Mitochondria** are the "power plants" of cells by virtue of their ability to carry out the energy-releasing aerobic metabolism of carbohydrates and fatty acids, capturing the energy in metabolically useful forms such as ATP. **Chloroplasts** endow cells with the ability to carry out photosynthesis. They are the biological agents for harvesting light energy and transforming it into metabolically useful chemical forms.

### 1.3c Membranes Are Supramolecular Assemblies That Define the Boundaries of Cells

Membranes define the boundaries of cells and organelles. As such, they are not easily classified as supramolecular assemblies or organelles, although they share the properties of both. Membranes resemble supramolecular complexes in their construction because they are complexes of proteins and lipids maintained by noncovalent forces. **Hydrophobic interactions** are particularly important in maintaining membrane structure. Hydrophobic interactions arise because water molecules prefer to interact with each other rather than with nonpolar substances. The presence of nonpolar molecules lessens the range of opportunities for water–water interaction by forcing the water molecules into ordered arrays around the nonpolar groups. Such ordering can be minimized if the individual nonpolar molecules redistribute from a dispersed state in the water into an aggregated organic phase surrounded by water. The spontaneous assembly of membranes in the aqueous environment, where life arose and exists, is the natural result of the hydrophobic ("water-fearing") character of their lipids and proteins. Hydrophobic interactions are the creative means of membrane formation and the driving force that presumably established the boundary of the first cell. The membranes of organelles, such as nuclei, mitochondria, and chloroplasts, differ from one another, with each having a characteristic protein and lipid composition tailored to